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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,202	04/13/2006	Osamu Honmou	033873-0108	4131

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,202	HONMOU ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9,11-15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) *20-22,25 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9,11-15,17-19,23,24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 19 October 2009.

Claim Status

Claims 6, 8, 9, 11-15 and 17-30 are pending. Claims 1-5, 7 and 10 are cancelled. Claims 9 and 18 are amended. However, claims 20-22, 25 and 27-30 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 6, 8, 9, 11-15, 17-19, 23-24 and 26 are under current examination.

Priority

This application claims benefit as a 371 National Stage application of PCT/JP04/09386 (filed 06/25/2004). The application also claims benefit from foreign application, JAPAN 2003-432329 (filed 12/26/2003). Accordingly, the instant application has been granted the benefit date, 26 June 2003, from foreign application, JAPAN 2003-432329.

RESPONSE TO ARGUMENTS

35 USC § 102

Mahmood

The rejection of claims 9, 11-15 and 17-19 under 35 USC 102(b) as anticipated over Mahmood et al. (Neurosurgery, Vol.49, No.5, November 2001: 1196-1204) is withdrawn in response to the applicant's claim amendments.

The applicant's arguments have been fully considered and are persuasive. The applicant has amended the claim such that the mesenchymal stem cells are recombinant mesenchymal stem cells. Mahmood does not anticipate this limitation.

Therefore, the examiner hereby withdraws the rejection of claims 9, 11-15 and 17-19 under 35 USC 102(b) as anticipated over Mahmood et al.

Kazuhiko

The rejection of claims 6, 8, 9, 11-13, 15-19, 23-24 and 26-27 under 35 USC 102(a) as anticipated by Kazuhiko et al (Molecular Therapy. Feb 2004. 9(2): 189-197) is withdrawn in response to the applicant's arguments.

The applicant's arguments have been fully considered and are persuasive. The applicant has perfected the claim to priority by submitting a certified copy of the foreign priority document, JAPAN 2003-432329. Accordingly, Kazuhiko et al. can no longer be considered prior art.

Therefore, the examiner hereby withdraws the rejection of claims 6, 8, 9, 11-13, 15-19, 23-24 and 26-27 under 35 USC 102(a) as anticipated by Kazuhiko et al

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Mahmood

Claims 6, 8, 9, 11-15, 17-19, 23-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahmood et al. (Neurosurgery, Vol.49, No.5, November 2001: 1196-1204) in view of Chen et al. (Neuropharmacology. 2000; 39: 711-716).

Claim 9 is directed to a method for treating a cranial nerve disease comprising the *in vivo* administration to a patient of a therapeutically effective amount of a cranial nerve disease therapeutic agent for *in vivo* administration, comprising a mesenchymal cell as an active ingredient, wherein the mesenchymal stem cell is: (a) a mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising a BDNF

gene, PLGF gene, GDNF gene, or IL-2 gene; or (b) an immortalized mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising an hTERT gene.

Mahmood et al. teach "stem cells for non-hematopoietic tissues are…referred to as marrow stromal cells (MSCs). MSCs are multipotent and can differentiate into…brain cells" (Page 1196, col.1.). In addition, the examiner notes that the art often refers to mesenchymal stem cells as marrow stromal cells. Mahmood et al. teach, "transplantation studies in cerebral ischemia, functional outcome was significantly improved in MSC-transplanted rats compared with bone marrow-transplanted animals….Bone marrow or MSCs transplanted directly into the striatum and cortex of rat brain subjected to TBI or middle cerebral artery occlusion migrate…induce neurological and functional improvement… Intravenous transplantation has the advantage of carrying the cells over a much wider area." (page 1196, col.2). MSC is an acronym for marrow stromal cells. Mesenchymal progenitor cells are components of bone marrow stroma. Mahmood et al. specifically describe mesenchymal cells administered by IV methods (page 1200, col.2). Accordingly, Mahmood teach administration of mesenchymal stem cells to treat neurological disease.

Further, Mahmood teaches, "Functional benefit obtained from central nervous system transplantation is due possibly to two different mechanisms, one being the functional integration of transplanted tissue into the neural circuitry and one being the production of trophic factors, cytokines, and other neural restorative factors. The latter may be responsible for the benefits observed early after transplantation, whereas the former may be the basis for late improvement. Transplanted MSCs may also interact

with the host brain and lead to the production of trophic factors, which contribute to recovery of function lost because of injury….The cytokines produced by MSCs may directly promote tissue plasticity or stimulate glial cells to produce neurotrophic growth factors such as brain-derived neurotrophic factor and nerve growth factor." (page 1201, col.1, parag. 1, emphasis added by examiner). In addition, Mahmood teaches, "MSC transplantation is clinically employed as both cell therapy and gene therapy in patients with severe osteogenesis imperfecta and in patients with cancer. Our work is a pioneering attempt to utilize MSC as a therapy for TBI" (page 1201, col.1, last parag.). Accordingly, Mahmood teach that production of BDNF at the site of mesenchymal stem cell integration into central nervous system transplantation is beneficial. Furthermore, Mahmood teach that production of trophic factors such as BDNF contribute to recovery of function lost because of injury. Finally, Mahmood suggests that mesenchymal stem cells can be used vehicles for delivery of therapeutic genes treating traumatic brain injury.

Therefore, Mahmood et al. suggest motivation to a skilled artisan for providing a mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising a BDNF gene in a method of treating a neurological disease using a recombinant mesenchymal stem cell. Accordingly, Mahmood et al. suggest the agents of claims 6 and 8.

The specification states, "the term 'mesenchymal cells' preferably refers to, for example, bone marrow cells (mononuclear cell fraction of bone marrow cells; MCF (mononuclear cell fraction)), cord blood cells, peripheral blood cells, mesenchymal stem

cells (MSCs), or cells derived from these cells." (page 5, lines 30-32). The specification further indicates that "mesenchymal stem cells may differentiate…via stromal cells into nerves" (page 6, lines 6-8). Because the specification indicates that marrow stromal cells are derived from mesenchymal stem cells, the examiner believes the teachings of Mahmood et al. satisfy the limitation of "mesenchymal cells" as taught by the specification.

Claim 11 is directed to the method of claim 9, wherein the cranial nerve disease is cerebral infarction. The examiner concludes Mahmood's treatments of the cerebral artery occlusion satisfy this claim.

Claim 12 is directed to the method of claim 9, wherein the in vivo administration is intravenous administration. Mahmood et al. specifically describe mesenchymal cells administered by IV methods (page 1200, col.2).

Claim 13 is directed to the method of claim 9, wherein the mesenchymal cell is a bone marrow cell, a cord blood cell, or a peripheral blood cell. Mahmood et al. teach mesenchymal cells from bone marrow.

Claim 14 is directed to the method of claim 13, wherein the bone marrow cell is an autologous cell of the patient. Mahmood et al. teach autologous MSCs (page 1200, col.2).

Claim 15 is directed to the method of claim 11, wherein the severe cerebral infarction is in a hyper acute stage of an acute stage. The specification does not define acute or hyperacute stage cerebral infarction. Therefore, the examiner asserts that Mahmood's treatments the cerebral artery occlusion satisfy this limitation of claim 15.

Claim 17 is directed to the method of claim 11, wherein the cranial nerve disease therapeutic agent is administered to a patient at any one of the times selected from:...a) within 72 hours from the onset of a cerebral infarction of a several cerebral infarction. Mahmood et al. teach administration of mesenchymal cells 24 hours after traumatic brain injury (abstract).

Claim 18 is directed to a method for neuroprotection of a cranial nerve disease patient comprising in vivo administration to a patient of a therapeutically effective amount of an agent comprising a mesenchymal cell as an active ingredient. The specification suggests that examples of cranial nerve diseases include "cerebral infarction, spinal cord injuries and demyelinating diseases" (page 4, lines 1-2). The examiner believes Mahmood's description of transplantation of mesenchymal cells into rat brains affected by cerebral artery occlusion satisfy this claim.

Claim 19 is directed to a method for regenerating the cranial nerve of a cranial nerve disease patient comprising the in vivo administration to a patient of a therapeutically effective amount of an agent comprising a mesenchymal cell as an active ingredient. Mahmood et al. teach "survival and growth of the graft within the brain" (page 1196, col.2).

Claim 23 is directed to a method for delivering therapeutic genes to a neurological disease site of a patient with neurological disease, comprising the *in vivo* administration of a therapeutically effective amount of mesenchymal stem cells to a patient in need thereof. Mahmood et al. suggest motivation to a skilled artisan for providing a mesenchymal stem cell that has been treated *ex vivo* with a transfection

vector comprising a BDNF gene in a method of treating a neurological disease using a recombinant mesenchymal stem cell. Accordingly, Mahmood et al. suggest *in vivo* administration a mesenchymal stem cell transfected with a vector comprising a BDNF gene.

Claim 24 is directed to the method of claim 23, wherein the neurological disease is cerebral infarction. The examiner concludes Mahmood's treatments of the cerebral artery occlusion satisfy this claim.

Claim 26 is directed to the method of claim 24, wherein the *in vivo* administration is intravenous administration. Mahmood et al. suggest IV administration (title).

While a skilled artisan would interpret the teachings of Mahmood as suggesting administration of a mesenchymal stem cell transfected with a vector comprising a BDNF gene for treatment of neurological disease, the explicit suggestion for combining BDNF and mesenchymal stem cells is not present in Mahmood.

Therefore, the examiner provides Chen et al. who demonstrate that grafting a combination of BDNF and bone marrow mesenchymal stem cells enhances differentiation of the cells into neurons (abstract). Furthermore, Chen suggests that bone marrow mesenchymal stem cells are useful as a vehicle for gene therapy for neurotransplantation and suggest that such cells can be genetically engineered (page 715, col.2, last parag). Accordingly, a skilled artisan would take the teachings and suggestions of Chen et al. as suggesting that he use a mesenchymal stem cell transfected with a vector comprising a BDNF gene in the methods of treating a neurological disease.

Therefore, Chen et al. suggest motivation to a skilled artisan for providing a mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising a BDNF gene in a method of treating a neurological disease using a recombinant mesenchymal stem cell. Accordingly, Chen et al. suggest the agents of claims 6 and 8.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to use a mesenchymal stem cell transfected with a vector comprising a BDNF gene in the methods of treating a neurological disease.

The person of ordinary skill in the art would have been motivated to make that modification to use a mesenchymal stem cells transfected with a vector comprising a BDNF gene in the methods of Mahmood because Mahmood indicates that BDNF is beneficial for integration of mesenchymal stem cells into the CNS and Mahmood further suggests that MSC has been used as a delivery vehicle for therapeutic genes. Additionally, Chen suggest making genetically engineered bone marrow mesenchymal stem cells for use in methods of treating stroke. Chen further indicates the benefit of co-administering both BDNF and bone marrow mesenchymal stem cell when performing transplantation to the CNS. Additionally, Chen suggest gene therapy methods of treating neurological diseases using neurotrophic factors, such as bone-derived neurotrophic factor (BDNF).

In addition to the teaching, suggestion and motivation provided in the cited art, there is a further rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and

one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (benefit of combining mesenchymal stem cells and BDNF in transplantation for treatment of neurological disease; suggestion of MSC transfected with a vector comprising a BDNF gene) are taught by Mahmood or Chen and further they are shown to be used in treatment of neurological disease. It would be therefore predictably obvious to use a combination of these elements in a method for treating neurological disease.

An artisan would have expected success, because Mahmood et al. teach some measure of success using mesenchymal stem cells for treating rat models of cranial infarction/ischemia. Additionally, Chen et al. teach that the combination of BDNF and bone marrow mesenchymal stem cells is highly successful for treating neurological disease by transplantation. Furthermore, it is suggested that BDNF is beneficial for integration of mesenchymal stem cells into the CNS, so a skilled artisan would expect success using mesenchymal stem cells transfected with a vector comprising a BDNF gene.

Therefore, the product and method as taught by Mahmood et al. in view of Chen et al. would have been *prima facie* obvious over the product and method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633